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(54) Title: ANALYSIS METHOD

(57) Abstract: This invention relates to novel methods for the identification of genes and gene products that are implicated in certain disease states. According to the invention, there is provided a method for the identification of a gene that is implicated in a specific disease or physiological condition, said method comprising the steps of comparing: i) the transcriptome or proteome of a first specialised cell type that is implicated in the disease or condition under first and second experimental conditions; with ii) the transcriptome or proteome of a second specialised cell type under said first and said second experimental conditions; and identifying as a gene implicated in the disease or physiological condition, a gene that is differentially regulated in the two specialised cell types under the first and second experimental conditions. The invention also relates to novel genes and gene products identified using these methods.

CLAIMS

1. A method for the identification of a gene that is implicated in a specific disease or physiological condition, said method comprising the steps of:

a) comparing:

i) the transcriptome or proteome of a first specialised cell type that is implicated in the disease or condition under first and second experimental conditions; with

ii) the transcriptome or proteome of a second specialised cell type under said first and said second experimental conditions; and

b) identifying as a gene implicated in the disease or physiological condition, a gene that is differentially regulated in the two specialised cell types under the first and second experimental conditions.

2. A method according to claim 1, wherein said specialised cell types are selected from the group consisting of cardiomyocytes, endothelial cells, sensory neurons, motor neurons, CNS neurons, astrocytes, glial cells, schwann cells, mast cells, eosinophils, smooth muscle cells, skeletal muscle cells, pericytes, lymphocytes, tumor cells, monocytes, macrophages, foamy macrophages, granulocytes, synovial cells / synovial fibroblasts and epithelial cells.

3. A method according to claim 1 or claim 2, wherein said first and second experimental conditions differ in respect of the cellular microenvironment, or in respect of exposure to hormones, growth factors, cytokines, chemokines, inflammatory agents, toxins, metabolites, pH, pharmaceutical agents, hypoxia, anoxia, ischemia, imbalance of any plasma-borne nutrient, osmotic stress, temperature, mechanical stress, irradiation, cell-extracellular matrix interactions, cell-cell interactions, accumulations of foreign or pathological extracellular components, intracellular and extracellular pathogens, or a genetic perturbation.

4. A method according to any one of the preceding claims, wherein the first experimental conditions and second experimental conditions differ in that under the second experimental conditions, the cells are exposed to a physiological stimulus.

5. A method according to claim 4, wherein the physiological stimulus is a physiological, mechanical, temperature, chemical, toxic or pharmaceutical stress.

6. A method according to claim 5, wherein said physiological stress is hypoxia.

7. A method according to any one of the preceding claims, wherein said first and second experimental conditions are different genetic conditions.

8. A method according to claim 7, wherein said second experimental conditions differ from said first experimental conditions in that the expression of a genetic element is expressed at a different level in said second experimental conditions relative to the level of expression of the genetic element in said first experimental conditions.

9. A method according to claim 8, wherein said genetic element is heterologous to the specialized cell type.

10. A method according to any one of the preceding claims, wherein the transcriptomes of the specialized cell types are compared by a technique involving hybridization to a nucleic acid array, subtractive mRNA hybridisation, the serial analysis of gene expression (SAGE); the selective amplification via biotin- and restriction-mediated enrichment (SABRE); differential display; representational difference analysis (RDA); differential screening of cDNA libraries; Northern blotting; an RNAse protection assay; an S1-nuclease protection assays; RT-PCR; real time RT-PCR (Taq-man); EST sequencing; massively parallel signature sequencing (MPSS); or sequencing by hybridisation (SBH).

11. A method according to claim 10, wherein the transcriptomes are compared by hybridization to a nucleic acid array.

12. A substantially purified polypeptide, encoded by a gene implicated in a specific disease or physiological condition by a method according to any one of the preceding claims.

13. A substantially purified polypeptide, which polypeptide:

i) comprises the amino acid sequence as recited in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139, 141, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209;

ii) has an amino acid sequence encoded by a nucleic acid sequence recited in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200,

202, 204, 206, 208, 210, 212, 214 and 216, or has an amino acid sequence encoded by a gene identified from an EST recited in any one of these SEQ ID Nos;

iii) is a fragment of a polypeptide according to i) or ii), provided that said fragment retains a biological activity possessed by the full length polypeptide of i) or ii), or has an antigenic determinant in common with the polypeptide of i) or ii); or

iv) is a functional equivalent of a polypeptide of i), ii) or (iii).

14. A polypeptide according to claim 13, wherein said biological activity is a hypoxia-regulated activity.

15. A polypeptide according to claim 14, wherein the expression of the polypeptide is hypoxia-induced.

16. A polypeptide according to claim 15, which polypeptide:

i) comprises the amino acid sequence as recited in any one of SEQ ID Nos.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139 and 141;

ii) has an amino acid sequence encoded by a nucleic acid sequence recited in any one of SEQ ID Nos.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 and 144, or is encoded by a gene identified from an EST recited in any one of these SEQ ID Nos.;

iii) is a fragment of a polypeptide according to i) or ii), provided that said fragment retains a biological activity possessed by the full length polypeptide of i) or ii), or has an antigenic determinant in common with the polypeptide of i) or ii); or

iv) is a functional equivalent of a polypeptide of i), ii) or (iii).

17. A polypeptide according to claim 14, wherein the expression of the polypeptide is hypoxia-repressed.

18. A polypeptide according to claim 17, which polypeptide:

i) comprises the amino acid sequence as recited in any one of SEQ ID Nos.: 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209;

ii) has an amino acid sequence encoded by a nucleic acid sequence recited in any one of SEQ ID Nos.: 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192,

194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214 and 216, or is encoded by a gene identified from an EST recited in any one of these SEQ ID Nos.;

iii) is a fragment of a polypeptide according to i) or ii), provided that said fragment retains a biological activity possessed by the full length polypeptide of i) or ii), or has an antigenic determinant in common with the polypeptide of i) or ii); or

iv) is a functional equivalent of a polypeptide of i), ii) or (iii).

19. A polypeptide which is a functional equivalent according to part iv) of any one of claims 13-18, is homologous to the amino acid sequence as recited in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139, 141, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209 or is homologous to the amino acid sequence encoded by a nucleic acid as recited in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214 and 216, and has equivalent biological activity to that possessed by the full length polypeptide of i) or ii).

20. A fragment or functional equivalent according to any one of claims 13-19, which has greater than 50% sequence identity with the amino acid sequence as recited in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139, 141, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209 or with the amino acid sequence that is encoded by a nucleic acid as recited in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214 and 216, or with fragments thereof, preferably greater than 60%, 70%, 80%, 90%, 95%, 98% or 99% sequence identity.

21. A fragment as recited in any one of claims 13-20 having an antigenic determinant in common with a polypeptide according to part i) of any one of claims 13-18, which consists of 7 or more (for example,

8, 10, 12, 14, 16, 18, 20 or more) amino acid residues from the amino acid sequence as recited in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139, 141, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209 or the amino acid sequence encoded by a nucleic acid as recited in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214 and 216.

22. A purified and isolated nucleic acid molecule that encodes a polypeptide according to any one of claims 13-21.

23. A purified nucleic acid molecule according to claim 22, which consists of the nucleic acid sequence as recited in any one of SEQ ID Nos.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214 and 216, or is a redundant equivalent or fragment thereof.

24. A purified nucleic acid molecule which hydridizes under high stringency conditions with a nucleic acid molecule according to claim 22 or claim 23.

25. A vector comprising a nucleic acid molecule as recited in any one of claims 22-24.

26. A delivery vehicle comprising a nucleic acid according to any one of claims 22-24 or a vector according to claim 25.

27. A host cell transformed with a vector according to claim 25.

28. An antagonist ligand which binds specifically to a polypeptide according to any one of claims 13-21, preferably a ligand which inhibits the hypoxia-induced activity of said polypeptide.

29. An agonist ligand which binds specifically to a polypeptide according to any one of claims 13-21, preferably a ligand which augments or potentiates a hypoxia-induced activity of said polypeptide.

30. A ligand according to claim 28 or claim 29, which is an antibody.

31. A ligand according to claim 28 or claim 29, which is a peptide, a peptidomimetic, or a drug molecule, such as a small natural or synthetic organic molecule of up to 2000Da, preferably 800Da or less.

32. A polypeptide according to any one of claims 13-21, a nucleic acid molecule according to any one of claims 22-24, a vector according to claim 25 or a ligand according to claim 30 or 31, for use in therapy or diagnosis of disease.

33. A polypeptide, nucleic acid molecule, vector or ligand as recited in claim 32, wherein said disease is a hypoxia-regulated condition.

34. A polypeptide, nucleic acid molecule, vector or ligand as recited in claim 33, wherein said hypoxia-regulated condition is tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis, the biological response to hypoxia conditions (including processes such as glycolysis, gluconeogenesis, glucose transportation, catecholamine synthesis, iron transport or nitric oxide synthesis).

35. A substantially purified polypeptide, which polypeptide:

i) comprises the amino acid sequence as recited in any one of SEQ ID Nos: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 63, 67, 69, 73, 75, 77, 85, 87, 89, 91, 93, 95, 99, 103, 113, 115, 119, 121, 129, 131, 133, 137, 139, 141, 145, 151, 153, 157, 159, 163, 169, 181, 187, 201, 205, 207 and 209 or SEQ ID Nos.: 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485 and 487;

ii) has an amino acid sequence encoded by a nucleic acid sequence recited in any one of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 92a, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200,

202, 204, 206, 208, 210, 212, 214 and 216, or has an amino acid sequence encoded by a gene identified from an EST recited in any one of these SEQ ID Nos;

iii) is a fragment of a polypeptide according to i) or ii), provided that said fragment retains a biological activity possessed by the full length polypeptide of i) or ii), or has an antigenic determinant in common with the polypeptide of i) or ii); or

iv) is a functional equivalent of a polypeptide of i), ii) or (iii).

for use in the diagnosis or therapy of the disease or abnormal physiological condition that is affected by hypoxia, such as cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis, hair loss, or the biological response to hypoxia conditions, including processes such as glycolysis, gluconeogenesis, glucose transportation, catecholamine synthesis, iron transport and nitric oxide synthesis.

36. A purified and isolated nucleic acid molecule that encodes a polypeptide as recited in claim 35, for use in the diagnosis or therapy of for use in the diagnosis or therapy of a disease or abnormal physiological condition that is affected by hypoxia, such as cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis or hair loss.

37. A purified nucleic acid molecule as recited in claim 36, which consists of the nucleic acid sequence as recited in any one of SEQ ID Nos.: 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486 and 488, or which is a redundant equivalent or fragment thereof, for use in the diagnosis or therapy of a disease or abnormal physiological condition that is affected by hypoxia, such as cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis or hair loss.

38. A purified nucleic acid molecule which hydridizes under high stringency conditions with a nucleic acid molecule as recited in claim 36 or claim 37, for use in the diagnosis or therapy of a disease or

abnormal physiological condition that is affected by hypoxia, such as cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis, or hair loss.

39. A vector comprising a nucleic acid molecule as recited in any one of claims 36-38, for use in the diagnosis or therapy of a disease or abnormal physiological condition that is affected by hypoxia, such as cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis, or hair loss.

40. A ligand which binds specifically to, and which preferably inhibits the hypoxia-induced activity of, a polypeptide as recited in claim 35, for use in the diagnosis or therapy of tumourigenesis, angiogenesis, apoptosis, the biological response to hypoxia conditions, or a hypoxic-associated pathology.

41. A pharmaceutical composition suitable for modulating hypoxia and/or ischaemia, comprising a therapeutically-effective amount of a polypeptide as recited in any one of claims 13-21 or 35, a nucleic acid molecule according to any one of claims 22-24 or 36-38, a vector according to claim 25 or 39, or a ligand according to claim 30, 31 or 40, in conjunction with a pharmaceutically-acceptable carrier.

42. A pharmaceutical composition according to claim 41, wherein said pharmaceutically-acceptable carrier is a liposome.

43. A vaccine composition comprising a polypeptide as recited in any one of claims 13-21 or 35, a nucleic acid molecule as recited in any one of claims 22-24 or 36-38, or a vector according to claim 25 or 39.

44. A method of treating a disease in a patient in need of such treatment by administering to a patient a therapeutically effective amount of a polypeptide as recited in any one of claims 13-21 or 35, an antagonist of said polypeptide, or a nucleic acid molecule as recited in any one of claims 22-24 or 36-38.

45. A method of regulating tumourigenesis, angiogenesis, apoptosis, the biological response to hypoxia conditions, or a hypoxic-associated pathology in a patient in need of such treatment by administering to a patient a therapeutically effective amount of a polypeptide according to any one of claims 13-21 or 35, a nucleic acid molecule according to any one of claims 22-24 or 36-38, or a vector according to claim 25 or 39, or a ligand according to claim 30, 31 or 40 or a pharmaceutical composition according to claim 41 or 42.

46. A method according to claim 45, wherein, for diseases in which the expression of the natural gene or the activity of the polypeptide is lower in a diseased patient when compared to the level of expression or activity in a healthy patient, the polypeptide, nucleic acid molecule, ligand, compound or composition administered to the patient is an agonist.

47. A method according to claim 45, wherein, for diseases in which the expression of the natural gene or activity of the polypeptide is higher in a diseased patient when compared to the level of expression or activity in a healthy patient, the polypeptide, nucleic acid molecule, vector, ligand, compound or composition administered to the patient is an antagonist.

48. A polypeptide according to any one of claims 13-21 or 35, a nucleic acid molecule according to any one of claims 22-24 or 36-38, a vector according to claim 25 or 39, a ligand according to claim 30, 31 or 40 or a pharmaceutical composition according to claim 41 or 42, for use in the manufacture of a medicament for the treatment of a hypoxia-regulated condition.

49. A method of monitoring the therapeutic treatment of a disease or physiological condition in a patient, comprising monitoring over a period of time the level of expression or activity of polypeptide according to any one of claims 13-21 or 35, a nucleic acid molecule according to any one of claims 22-24 or 36-38, in tissue from said patient, wherein altering said level of expression or activity over the period of time towards a control level is indicative of regression of said disease.

50. A method of providing a hypoxia regulating gene, an apoptotic or an angiogenesis regulating gene by administering directly to a patient in need of such therapy an expressible vector comprising expression control sequences operably linked to one or more of the nucleic acid molecules recited in claims 22-24 or 36-38.

51. A method of diagnosing a hypoxia-regulated condition in a patient, comprising assessing the level of expression of a natural gene encoding a polypeptide according to any one of claims 13-21 or 35, or assessing the activity of such a polypeptide, in tissue from said patient and comparing said level of expression or activity to a control level, wherein a level that is different to said control level is indicative of the hypoxia-related condition.

52. A method according to claim 51 that is carried out *in vitro*.

53. A method according to claim 51 or claim 52, which comprises the steps of: (a) contacting a ligand according to claim 30, 31 or 40 with a biological sample under conditions suitable for the formation of a ligand-polypeptide complex; and (b) detecting said complex.

54. A method according to claim 51 or claim 52, comprising the steps of:

a) contacting a sample of tissue from the patient with a nucleic acid probe under stringent conditions that allow the formation of a hybrid complex between a nucleic acid molecule according to any one of claims 22-24 or 36-38 and the probe;

b) contacting a control sample with said probe under the same conditions used in step a); and

c) detecting the presence of hybrid complexes in said samples;

wherein detection of levels of the hybrid complex in the patient sample that differ from levels of the hybrid complex in the control sample is indicative of the hypoxia-related condition.

55. A method according to claim 51 or claim 52, comprising the steps of:

a) contacting a sample of nucleic acid from tissue of the patient with a nucleic acid primer under stringent conditions that allow the formation of a hybrid complex between a nucleic acid molecule according to any one of claims 22-24 or 36-38 and the primer;

b) contacting a control sample with said primer under the same conditions used in step a);

c) amplifying the sampled nucleic acid; and

d) detecting the level of amplified nucleic acid from both patient and control samples;

wherein detection of levels of the amplified nucleic acid in the patient sample that differ significantly from levels of the amplified nucleic acid in the control sample is indicative of the hypoxia-related condition.

56. A method according to claim 51 or claim 52, comprising the steps of:

a) obtaining a tissue sample from a patient being tested for the hypoxia-related condition;

b) isolating a nucleic acid molecule according to any one of claims 22-24 or 36-38 from said tissue sample; and

c) diagnosing the patient for disease by detecting the presence of a mutation which is associated with the hypoxia-related condition in the nucleic acid molecule as an indication of the hypoxia-related condition.

57. The method of claim 56, further comprising amplifying the nucleic acid molecule to form an amplified product and detecting the presence or absence of a mutation in the amplified product.

58. A method according to any one of claims 49-57, wherein said disease is cancer, ischaemic conditions, reperfusion injury, retinopathy, neonatal stress, preeclapmsia, atherosclerosis, inflammatory

conditions, wound healing, tumourigenesis, angiogenesis, apoptosis, inflammation, erythropoiesis, or hair loss.

59. A method according to claim 58, wherein said hypoxia or ischaemia-related tissue damage is due to a disorder of the cerebral, coronary or peripheral circulation.

60. A method according to any one of claims 49, and 54-59, wherein the tissue is a cancer tissue.

61. A method for the identification of a compound that is effective in the treatment and/or diagnosis of disease, comprising contacting a polypeptide according to any one of claims 13-21 or 35, a nucleic acid molecule according to any one of claims 22-24 or 36-38 with one or more compounds suspected of possessing binding affinity for said polypeptide or nucleic acid molecule, and selecting a compound that binds specifically to said nucleic acid molecule or polypeptide.

62. A method for the identification of a compound that is effective in the treatment and/or diagnosis of disease, comprising contacting a cell or cell membrane preparation comprising a polypeptide according to any one of claims 13-21 or 35 or a nucleic acid molecule according to any one of claims 22-24 or 36-38 with one or more candidate compounds and detecting the degree of compound binding, or the stimulation or inhibition of a functional response in said cell or cell membrane.

63. A compound identified or identifiable by a method according to claim 61 or claim 62.

64. A compound according to claim 63, which is a natural or modified substrate, an enzyme, a receptor, a small organic molecule, such as a small natural or synthetic organic molecule of up to 2000Da, preferably 800Da or less, a peptidomimetic, an inorganic molecule, a peptide, a polypeptide, an antibody, or a structural or functional mimetics of any of these compounds.

65. A kit useful for diagnosing disease comprising a first container containing a nucleic acid probe that hybridises under stringent conditions with a nucleic acid molecule according to any one of claims 22-24 or 36-38; a second container containing primers useful for amplifying said nucleic acid molecule; and instructions for using the probe and primers for facilitating the diagnosis of disease.

66. The kit of claim 65, further comprising a third container holding an agent for digesting unhybridised RNA.

67. An array of at least two nucleic acid molecules, wherein each of said nucleic acid molecules either corresponds to the sequence of, is complementary to the sequence of, or hybridises specifically to a nucleic acid molecule according to any one of claims 22-24 or 36-38.

68. An array according to claim 67, which contains nucleic acid molecules that either correspond to the sequence of, are complementary to the sequence of, or hybridise specifically to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 92a, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294 or 295 of the nucleic acid molecules implicated in a hypoxia-regulated condition as recited in claims 22-24 or 36-38.

69. An array according to any claim 67 or claim 68, wherein said nucleic acid molecules consist of between twelve and two thousand nucleotides.

70. An array of antibodies, comprising at least two different antibody species, wherein each antibody species is immunospecific with a polypeptide implicated in a hypoxia-regulated condition as recited in any one of claims 13-21 or 35.

71. An array of polypeptides, comprising at least two polypeptide species as recited in any one of claims 13-21 or 35, wherein each polypeptide species is implicated in a hypoxia-regulated condition, or is a functional equivalent variant or fragment thereof.

72. A kit comprising an array of nucleic acid molecules according to any one of claims 67-69.

73. A kit comprising one or more antibodies that bind to a polypeptide as recited in any one of claims 13-21 or 35; and a reagent useful for the detection of a binding reaction between said antibody and said polypeptide.

74. A transgenic or knockout non-human animal that has been transformed to express higher, lower or absent levels of a polypeptide according to any one of claims 13-21 or 35.

75. A method for screening for a compound effective to treat disease, by contacting a non-human transgenic animal according to claim 74 with a candidate compound and determining the effect of the compound on the disease or physiological condition of the animal.

76. A substantially purified polypeptide comprising the consensus sequence: KAMVACYPGNGTGYVRHVDNPNGDGRCITCIYYLNKNWDAKLHGGILRIFPEGKSFIADVEPI FDRLLFFWSDRRNPHEVQPSYATRYAMTVWYFDAEERAEAKKK, or a variant thereof.

77. A substantially purified polypeptide according to claim 76, for use in the diagnosis or treatment of a hypoxia-related disease or condition.

LEFLVRNNVLLELLRSSLILLQGSWFFQIGFVLYPPSGGPAWDLMDHENILFLTICFCWHYAVTIVIVGMNYAFITWLVKSRLK
RLCSSEVGLLKNAEREQESEEEM

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GAAGCACATCTGGACAGCTGTGCGGCCTCCTTGCGGGCCGACGTCAGCCGAGCACGTCCCCCACGTCCTCTCCTTCTCGCCACT
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GTCCTTAACCAAGTTAATGTTGTCAAATGCCTTATTTGTGGAGGCCTTTATCTTCTACAACCACACTCATGGCCGGGAAATGCT
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MPSLWDRFSSSSTSSSPSSLPRTPTPDRPPRSAWGSATREEGFDRSTSLESSDCESLDSSNSGFGPEEDTAYLDGVSLPDFELL
SDPEDEHLCANLMQLLQESLAQARLGSRRPARLLMPSQLVSQVGKELLRLAYSEPCGLRGALLDVCVEQGKSCHSVGQLALDPS
LVPTFQLTLVLRLDSRLWPKIQGLFSSANSPFLPGFSQSLTLSTGFRVIKKKLYSSEQLLIEEC

26

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CAGCAAACGCCCTGGCGTCTGTCCTCACCATGCGTAGCCTTTGGGACCGCTTCTCGTCGTCGTCCACCTCCTCTTCGCCCTCGT
CCTTGCCCCGAACTCCCACCCCAGATCGGCCGCCGCGCTCAGCCTGGGGGTCGGCGACCCGGGAGGAGGGGTTTGACCGCTCCA
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